

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY  
DEPARTMENT OF PESTICIDE REGULATION  
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

DIURON

Chemical Code # 231, Tolerance # 106  
SB 950 # 018

December 8, 1986  
Revised 8/24/87, 7/12/88, 8/2/90, 9/26/92, 5/11/95 and 11/17/97

I. DATA GAP STATUS

Chronic toxicity, mouse:	No data gap, possible adverse effect
Chronic toxicity, dog:	No data gap, possible adverse effect
Oncogenicity, rat:	No data gap, possible adverse effect
Oncogenicity, mouse:	No data gap, possible adverse effect
Reproduction, rat:	No data gap, no adverse effect
Teratology, rat:	No data gap, no adverse effect
Teratology, rabbit:	No data gap, no adverse effect
Gene mutation:	No data gap, no adverse effect
Chromosome effects:	No data gap, possible adverse effect
DNA damage:	No data gap, no adverse effect
Neurotoxicity:	Not required at this time

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Toxicology one-liners are attached.

All record numbers for the above study types through 127140 (Document No. 106-048) were examined. This includes all relevant studies indexed by DPR as of March 2, 1995.

In the 1-liners below:

\*\* indicates an acceptable study.

**Bold face** indicates a possible adverse effect.

File name: T971117

Revised by C. Aldous, May, 1995; J. Gee, November 17, 1997 [no new data, supplemental study 1-liner added]

## II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may identify additional effects.

## COMBINED, RAT

**035 064725** "Diuron: Study for chronic toxicity and carcinogenicity with Wistar rats (Administration in diet for up to two years)". Institute of Toxicology, Bayer AG, Wuppertal, 10/29/85 (original German report), English translation, 7/14/86. Diuron, 98.7% purity, in feed of Wistar rats for 2 years. Levels of 0, 25, 250, and 2500 ppm for 50 rats/sex/treatment. No NOEL was obtained in this study: hematology parameters (RBC count, Hct, Hgb) and increased reticulocyte count, were suggestive of hemolytic anemia (LEL in F = 25 ppm). This was further substantiated by hemosiderin deposition in spleen and splenic enlargement (LEL in M and F = 25 ppm), and increased erythropoiesis in bone marrow and related signs at higher doses. Transitional epithelial cell carcinomas, especially in urinary bladder, were found in both sexes at 2500 ppm only. Epithelial cell tumors in renal pelvises of three 2500 males were probably also treatment-related. Marked hyperplasia was found in bladder and renal epithelium at 2500 ppm in M and F, also to a lesser extent in F at 250 ppm. Erythrocyte and tumor effects constitute **possible adverse effects**. Study does **not** satisfy chronic study data requirements (ophthalmology and histology of spinal cord are lacking). Adequacy of the rodent chronic study data base will be re-examined on receipt of an acceptable non-rodent chronic study. The 8/2/90 rebuttal response indicates that the study is sufficient to fill the **oncogenicity** data requirement. Note the related study (034:065390, Bayer AG study T 7018927, 8/1/86), which establishes a NOEL of 10 ppm for hematological effects. This 10 ppm NOEL is an appropriate value for chronic effects not associated with neoplasia. C. Aldous, 7/8/88, 8/2/90.

**\*\*106-042 091075** (addendum to record 106-035:064725, above). Weekly macroscopic examinations of rats for lenticular opacities and for corneal opacities were provided. No treatment effect was observed. New data do not allow an upgrade of the study, however the CDFA rebuttal response of 8/2/90 indicates that the study is sufficient to fill the rat "oncogenicity" data requirement. Aldous, 8/2/90.

**034 065390** (Subchronic study ancillary to combined study 035:064725) "Diuron: Toxicological study with Wistar rats paying special attention to effects on the blood (Administration in diet for six months)". Institute of Toxicology, Bayer AG, Wuppertal, 8/1/86 (original German report), English translation, 3/27/87. 10 Wistar rats/sex/dosage at 0, 4, 10, and 25 ppm Diuron (98.8%) in diet for 6 months. NOEL = 10 ppm (minor hematological changes, especially in females: increased iron pigment deposition in both sexes at 25 ppm). These data allow a NOEL of 10 ppm for non-oncogenic effects in the associated rat combined study 035:064725. C. Aldous, 7/11/88.

**016 036189 to -91**, "Chronic Feeding Studies of Diuron in Rats", (Univ. of Rochester School of Medicine and Dentistry, NY, 7/30/64). Two lots of Diuron, 80% a.i., no analysis included; fed to 35/sex/group for 2 years at 0, 25, 125, 250 or 2500 ppm. Decreased body weight gains in 250 and 2500 ppm groups; **possible adverse effects** of decreased hemoglobin, hematocrit, and erythrocyte counts with associated extramedullary hematopoiesis in the 250 and 2500 ppm females. NOEL = 125 ppm. **Unacceptable, not upgradeable** (inadequate number of animals at

risk, no serum chemistry, no analysis of diet, incomplete histopathology, inconsistent sites for harvest of marrow.) (Martz, 12/10/85)

EPA 1-liner: No CORE grade. Systemic NOEL = 25 ppm (slight anemia, enlarged spleens, increased erythrogenic activity in bone marrow and abnormal pigments in the blood.) NOTE: 1983 EPA Reregistration Guidance Document indicates that rodent chronic study data requirement is filled, citing this reference.

001 014740, "Oral Toxicity and Metabolism of Diuron (N-(3,4-Dichlorophenyl)-N,N'-dimethylurea) in Rats and Dogs", (University of Rochester School of Medicine and Dentistry.) Publication: Food Cosmet. Toxicol. 5: 513-531 (1967). Appears to be the same data as in 036189 above.

018 036196, 036201 and 036202 Summaries of 036189 - 91.

### CHRONIC TOXICITY, DOG

**\*\*106-043 095088** Hoffmann, K. and Schilde, B. "Diuron, Chronic Toxicity to Dogs after Oral Administration (12-month feeding study)", (Bayer AG, Institute of Toxicology, Wuppertal-Elberfeld, Report # 13325, 6/3/85), Diuron, 98.2% purity, fed in the diet for 12 months at 0 (control), 50, 300, and 1800 ppm with 6 Beagle (Bor:Beag) dogs/sex/group. Reduced mean erythrocyte counts, hemoglobin, hematocrit, MCHC, and alpha-1 and alpha-2 globulin values were noted in both sexes at 300 and 1800 ppm. Increased MCV values, Heinz' inclusion bodies in erythrocytes, reticulocytes, leukocytes, beta globulins, platelet, alanine aminotransferase activity, and alkaline phosphatase activity was reported in both sexes at 1800 ppm. Reactive fat-depleted bone marrow with increased siderin content and heightened hematogenic pigment deposits in livers, kidneys, and spleens were reported in both sexes at 1800 ppm. Increased relative spleen weights were noted in both sexes at 1800 ppm and in males at 300 ppm.

**Possible adverse effect:** hypochromic anemia. **NOEL = 50 ppm. Acceptable.** (Originally considered unacceptable, possibly upgradeable. Additional data in Record No. 127140 below were considered in re-evaluation. Green, Kellner and Gee, 9/21/92. Updated by Aldous, 5/11/95.

106-057 127140 (addendum to Document No. 106-043, Record No. 095088). Original study title: "Diuron: Chronic toxicity to dogs after oral administration (12-month feeding study)", Report # 13325. Additional data authors: Van Pelt, C.S., Hoffmann, K., and Schilde, B. Original study completed 6/3/85, present addendum dated 11/1/93. An examination of the additional data, coupled with inspection of the original report, allow the study report to be upgraded to **acceptable** status. There is no change in the interpretation of the study. Aldous, 5/11/95 (worksheet included).

**017 036195** "Chronic Feeding Studies of Diuron in Dogs", (Univ. of Rochester School of Medicine and Dentistry, NY, 7/30/64). Diuron, two lots, 80% WP (nominal); 3/sex/group Beagle dogs, except no females at 25 ppm, age not given, were fed 0, 25, 125, 250 or 2500/1250 ppm (high dose was 1250 ppm from week 3 onward) in the diet for two years. No analysis of diet provided; diets prepared weekly. **Possible adverse effects** include significant decreases in RBC, HGB and HCT in mid- and high-dose males and females, increased liver weight in high dose males, erythroid hyperplasia in marrow and hemosiderin accumulation in

reticuloendothelial cells in high dose males and females. **Unacceptable, not upgradeable** (lack of diet analysis for content and stability under use conditions, no food consumption - both of which prevent determination of actual compound intake for establishment of a NOEL, no ophthalmology exams, other deficiencies as indicated in review by F. Martz. (Martz 12/9/85, C. Aldous 7/11/88).

EPA 1-liner: No CORE grade. Systemic NOEL = 25 ppm (abnormal pigments in the blood.)

NOTE: 1983 EPA Reregistration Guidance Document indicates that the dog chronic study data requirement is filled, citing this reference.

018 036200 An interpretative summary of 017:036195, above.

001, 003 041964 Same study as 036195, published in Food Cosmet. Toxicol. 5: 513-531 (1967). J. Schreider noted "insufficient information for assessment", 3/1/85.

#### ONCOGENICITY, RAT

See under Combined Rat above.

#### COMBINED (CHRONIC + ONCOGENICITY) MOUSE

**\*\*106-048 097889** Eiben, R. "Diuron: Study for Chronic Toxicity and Carcinogenicity with NMRI Mice (Administration in Diet for 24 Months)", (Bayer Agricultural Institute of Toxicology, Wuppertal, West Germany, du Pont Report # DIUR/TOX9, October 1983). Diuron technical, 98.7% purity, was administered in the diet for 24 months at 0 (control), 25, 250, and 2500 ppm to SPF-bred mice (Bor strain NMRI SPF HAN) with 60/sex/group (10/sex/group for interim sacrifice). Body weights were approximately 10% less in 2500 ppm dose group compared to control; increased relative liver and spleen weight in 2500 ppm males at 12 and 24 months was indicated. Biochemical changes related to liver lesions (increased alanine-aminotransferase activity, glucose and bilirubin). Liver lesions consisted of centrilobular hepatopathy and increased iron pigment deposition (hemosiderosis) in the high-dose mice. Significantly elevated mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), reticulocytes, platelets and leucocytes were noted in this group. **Possible adverse effect:** increased incidence of female mammary adenocarcinomas at 2500 ppm. **Acceptable.** Chronic NOEL = 250 ppm (hematological, liver effects and bladder hyperplasias in females). Green, Kellner and Gee, 9/16/92.

#### REPRODUCTION RAT

**\*\*106-047 095880** Cook, J. "Reproductive and Fertility Effects with Diuron (IN 14740) Multigeneration Reproduction Study in Rats", (E. I. du Pont de Nemours and Company, Haskell Laboratory for Toxicology and Industrial Medicine, Report 560-90, 12/14/90). Diuron technical (lot 8805540, 97.1% purity) was fed in the diet to 30 Crl:CD\*BR rats/dose/sex for two generations at 0 (control), 10, 250, and 1750 ppm. F0 animals were fed treated diet 73 days prior to mating and F1 animals received treatment diet for at least 105 days after weaning and

prior to mating. Decreased F0 and F1 body weights (5% to 20% less than controls) and food consumption at 1750 ppm was indicated. **No Adverse Effects.** Parental NOEL = 250 ppm (reduced F0 and F1 body weights and food consumption at 1750 ppm). Reproductive NOEL = 250 ppm (reduced F1 and F2 pup weights at 1750 ppm). **Acceptable.** (Green, Kellner and Gee, 9/18/92).

016 036192, -93, -97 and -98, "Reproduction Study in Rats Fed Diuron (and) Second Reproduction Study in Rats Fed Diuron", (Univ. of Rochester School of Medicine and Dentistry, 7/30/64). Two lots of Diuron, 80%, were fed to 8 males/16 females per group at 0 or 125 ppm. Two studies were performed with the same numbers of animals. No adverse reproductive effect reported in the repeat study but postweaning growth retardation was noted in the first one. The reason for the difference remains undetermined. NOEL cannot be determined because of deficiencies in the reports. Unacceptable, not upgradeable (no analysis of diet, no food consumption, single dose, inadequate number of pregnant animals, parental animals were not necropsied.) (Martz 12/10/85)

EPA 1-liners: No CORE grades. Reproductive NOEL > 125 ppm (single dose tested). In the first study, systemic NOEL < 125 ppm (body weight depression observed at F2b and F3a litters). Systemic NOEL in second > 125 ppm. NOTE: 1983 EPA Reregistration Guidance Document indicates that this study fills the rat reproduction study data requirement.

001 038724 Summary in publication of 036192 and associated records, above. Hodge, H. C. et al., Food Cosmet. Toxicol. 5: 513-531 (1967).

#### TERATOGENICITY RAT

\*\*025 051033, "Developmental Toxicity Study of H-16035 Administered by Gavage to Rats", (Argus Research Laboratories, Inc., Horsham, PA., # HLO 410-86, 6/16/86), H-16035 (diuron) 99.0%, purity and stability contained in sponsor's records; administered in aqueous 0.5% hydroxypropyl methylcellulose by gavage at 0, 16, 80, or 400 mg/kg/day, 25 mated females/group, on days 6 through 15 of gestation (day 0 = sperm and/or plug). Reduced feed consumption, reduced maternal body weight and body weight gain at 80 and 400 mg/kg/day. Reduced fetal body weight and delayed ossification at 400 mg/kg/day. No adverse developmental effects. NOEL (maternal) = 16 mg/kg/day, (developmental) = 80 mg/kg/day. Acceptable. (Carlisle 7/24/87)

001, 020 036209, "Teratogenicity Studies on Pesticidal Formulations of Dimethoate, Diuron and Lindane in Rats", (Publication: Bull. Envir. Contam. Toxicol. 22: 522-529 (1979) by Khera, K. S. et al.). Karmex containing 80% diuron, given in corn oil to 20 female Wistar rats per group by oral gavage, days 6 to 15 of gestation, at 0, 125, 250 or 500 mg/kg/day. Unacceptable, upgradeable (lacking in methods and data). Apparent NOEL < 125 mg/kg. Fetal weight was reduced in the high dose group and wavy ribs were noted in the mid- and high-dose groups. The incidence in the controls was 3 and 7 in each of the mid- and high-dose groups. The number of fetuses examined for skeletal findings was 2/3's of the total number but the actual figure is not given. The total number of all fetuses was 199, 164 and 147 in the control, mid-and high-dose groups. No individual data is included for evaluation. Apparent maternal NOEL = 250 (reduced body weight.) (Schreider 3/1/85, Martz 12/10/85)

NOTE: Dr. Schreider noted "possible adverse effect" (effects of possible "borderline significance"), however both he and Martz noted "insufficient information for assessment" or "information supplementary only". The subsequent submission of an acceptable study

(025:051033, above), which demonstrated that developmental effects were not observed until a definitively maternally toxic dose was achieved, removes concerns about developmental toxicity in this study. (C. Aldous, 7/12/88)

EPA 1-liner: Supplementary. Teratogenic NOEL > 500 mg/kg (HDT). Fetotoxic NOEL < 125 mg/kg (developmental toxicity).

### TERATOGENICITY, MOUSE

003, 020 036208, "Teratogenicity of Pesticides". Chapter 8. Report of the Secretary's Commission on Pesticides and Their Relationship to Environmental Health. US EPA, December, 1969. (Publication, 1969). Only data are in Table 3 in which diuron is stated to be negative in 6 litters at 215 mg/kg. Unacceptable. (Schreider 3/4/85, Martz 11/25/85)

### TERATOGENICITY, RABBIT

\*\*026 051034, "Developmental Toxicity Study of H-16035 Administered by Gavage to New Zealand White Rabbits", (Argus Research Laboratories, Inc., Horsham, PA., # HLO-332-86, 5/6/86), H-16035 (diuron) 99.0%, in aqueous 0.5% hydroxypropyl methylcellulose administered by gavage on days 7 through 19 of gestation to artificially-inseminated females, 23, 24 or 25/group, at 0, 2, 10, or 50 mg/kg/day. Maternal toxicity (decreased feed consumption and weight gains and 1 abortion) at 50 mg/kg/day. No adverse developmental effects. NOEL (maternal) = 10 mg/kg/day, (developmental)  $\geq$  50 mg/kg/day. Acceptable. (J. Carlisle, 7/24/87)

### MUTAGENICITY: Gene Mutation

#### Microbial Systems

\*\*019, 013 036206, "Mutagenicity Evaluation in Salmonella typhimurium", (Haskell Lab, Report No. 471-84, 11/9/84) Diuron, 98%; tested in Salmonella strains TA1535, TA97, TA98 and TA100 with rat liver activation at 0, 10, 25, 50, 100 or 250 ug/plate and without activation at 0, 0.5, 1, 2.5, 5 or 10 ug/plate in duplicate, two trials; no increase in reversion rate reported; cytotoxicity with TA1535; acceptable. (Schreider 3/1/85, Remsen (Gee) 12/16/85)

#### Mammalian cells

\*\* 019 036204, "Mutagenicity Evaluation of Diuron in the CHO/HGPRT Assay", (Haskell Labs, Report No. 282-85, 6/28/85.), Diuron, 98.19%; tested in CHO cells at 0, 0.01, 0.5, 1.0, 1.125, 1.25 or 0.5 mM; 18-20 hours without activation, 5 hours with rat liver activation; duplicates, 3 trials; no increase in mutation frequency. Acceptable. (Remsen (Gee) 12/11/85)

### MUTAGENICITY, CHROMOSOME

\*\* **019 036205**, "In vivo Assay of Diuron for Chromosome Aberrations in Rat Bone Marrow Cells". Haskell Labs, Report No. 366-85, 6/26/85. Sprague-Dawley rats. Diuron, 98.19%, given by oral gavage in a single dose of 0, 50, 500 or 5000 mg/kg to 15/sex/group; 5/sex/group were

sacrificed at 6, 24 or 48 hours; 50 metaphases per rat scored; at high dose, weight loss, mitotic index decreased and average number of aberrations increased in the 48-hour sampling - no difference at 6 hours, questionable effect at 24 hours. Acceptable. (J. Remsen (Gee) 12/11/85)

#### MUTAGENICITY, DNA/OTHER

\*\*019, 025 036207, 051032, "Assessment of Diuron in the In vitro Unscheduled DNA Synthesis Assay in Primary Rat Hepatocytes", (Haskell Labs, Report No. 349-85, 7/10/85), diuron technical 98.19%, lot # T-50906; dissolved in DMSO and tested at 0, 0.001, 0.010, 0.1, 0.33, 1.0, or 20 mM with  $5 \times 10^5$  rat hepatocytes/well, 6 wells/plate/dose; 2 trials; positive control DMBA. Cytotoxicity at 0.33 mM and above with a decrease in cytoplasmic grain counts and an increase in nuclear grain counts. No UDS reported. Initially reviewed by J. Remsen (Gee), 12/11/85 as unacceptable with insufficient information to assess. Re-reviewed by J. Carlisle, 7/24/87. Additional information (025 051032) led to change in status to acceptable with no adverse effects.

#### NEUROTOXICITY

Not required at this time.

#### SUPPLEMENTAL STUDY

**210-054 148807** " Mouse bone marrow micronucleus assay of DPX-M2574-43 (Krovar® IDF)" (L. R. Cox, Study Director; Haskell Laboratory for Toxicology and Industrial Medicine, du Pont, No. 685-95, 6/12/96) DPX-M2574-43, Krovar®IDF), a mixture of bromacil and diuron, was given as a single acute dose by gavage to Crl:CD-1®(ICR)BR mice. Males were given 1000 mg/kg and females, 750 mg/kg. Six treated animals per sex were sampled at 24, 48 and 72 hours post-dosing. Cyclophosphamide was the positive control at 24 hours. 0.5% methylcellulose was the vehicle control, 5/sex, at 24, 48 and 72 hours. The incidence of micronucleated polychromatic erythrocytes in 2000 PCEs per animal were scored. There was a statistically significant increase in the incidence in treated females at 48 hours. The incidence was 0.51 in treated mice versus 0.27 in controls. Cyclophosphamide was functional. The study is considered positive. **Possible adverse effect.** The study is SUPPLEMENTAL because the test material was a mixture of 2 active ingredients. (Gee, 11/14/97)